General

Guideline Title

Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan 27. 44 p. (Technology appraisal guidance; no. 377).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- In people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- And only when the company provides it with the discount agreed in the patient access scheme

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Metastatic hormone-relapsed prostate cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Oncology

Urology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated

Target Population

Adult men with metastatic hormone-relapsed prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated

Interventions and Practices Considered

Enzalutamide

Major Outcomes Considered

- Clinical effectiveness
  - Overall survival
  - Radiographic progression-free survival (rPFS)
  - Time to initiation of cytotoxic chemotherapy
  - Time to prostate specific antigen (PSA) progression
  - PSA response (decrease in >50% and >90%)
  - Best overall soft tissue response
  - Adverse events of treatment
  - Health-related quality of life (HRQOL)
  - Time to treatment discontinuation (TTD)
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Aberdeen Health Technology Assessment (HTA) Group (see the "Availability of Companion Documents" field). See section B of the manufacturer's submission (see the "Availability of Companion Documents" field) for details on search strategies.

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The company undertook comprehensive searches to identify relevant clinical effectiveness data and the strategies are reproduced in full in the submission. Sources searched were extensive and included relevant conference proceedings and trials registers. The search strategies used were designed to include information for the European Medicines Agency (EMA) submission and were therefore broader than the scope of this submission, including additional interventions and not restricting by study design (apart from the EMBASE search) or outcomes. A comprehensive range of controlled vocabulary and free text terms were used and combined appropriately using Boolean logic. The ERG believes that all relevant data were retrieved by these searches.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria applied by the company for the systematic review of clinical effectiveness are detailed below. The ERG believes the criteria are comprehensive and in keeping with the NICE final scope.

Inclusion Criteria

Population

Studies in adults (over the age of 18) with asymptomatic, or mildly symptomatic, metastatic hormone-relapsed prostate cancer and who have not received prior chemotherapy, were eligible for inclusion in the review.*

Interventions

The interventions were enzalutamide, abiraterone, docetaxel, radium-223 dichloride and sipuleucel-T. However, only studies including enzalutamide or abiraterone as an intervention or comparator are described in the review.

Outcomes

- The outcomes included in the systematic literature review included overall survival (OS), progression-free survival (PFS), radiographic PFS (rPFS), response rate, prostate specific antigen (PSA) response, time to chemotherapy initiation, time to antineoplastic therapy (cytotoxic or hormonal), time to skeletal-related event (SRE), time to PSA progression, best overall response, adverse effects of treatment, health-related quality of life (HRQL) including time to pain progression, time to increase in analgesia and time to decline in performance status.
- Of the outcomes listed above, only OS, rPFS, time to chemotherapy initiation, time to SRE, time to PSA progression and overall best response were to be included in the indirect treatment comparison.

Study Design

- Phase II and III, randomised controlled trials (RCTs) of any size and duration were eligible for inclusion in the clinical effects and safety review.

- Crossover RCTs were eligible if data were presented at crossover.
- Non-randomised comparative and uncontrolled studies were eligible for inclusion if they reported relevant clinical effectiveness or safety data for enzalutamide.
- Studies published as abstracts or conference presentations, as well as data from unpublished RCTs, were eligible for inclusion in the review if adequate data were provided. Systematic reviews were eligible for inclusion as a source of references to primary studies.

Language Restrictions

Studies reported in languages other than English were identified and listed for information only.

*Studies assessing mixed populations (i.e., where some patients had received chemotherapy and some had not) were included in the indirect treatment comparison for comparators where studies of chemotherapy naïve populations did not exist. However, the only study included for the indirect comparison versus abiraterone had enrolled chemo-naïve patients only.

Exclusion Criteria

Population

Studies reporting on patients described as 'hormone sensitive' or 'castration sensitive' were not eligible for inclusion. Similarly, studies reporting on patients who had received prior chemotherapy were excluded.

Interventions

Studies that did not include any of the interventions listed in the inclusion criteria

Outcomes

Studies that did not include any of the outcomes listed in the inclusion criteria

Study Design

Single arm studies except if they provided relevant clinical effectiveness or safety data for enzalutamide

Language Restrictions

No study reported in any language other than English was reviewed or included in the indirect treatment comparison.

The PRISMA flow chart detailing the number of studies included and excluded by the company is presented as Figure 3 in the ERG report. After reasonable exclusions, the company identified one, triple-blind phase III RCT of enzalutamide compared with placebo, the PREVAIL trial.

One relevant non-RCT was identified. This is a dose escalation study of enzalutamide, which includes a mixed population of chemotherapy-naïve (n=12) and post-chemotherapy (n=12) patients. The study does not report data separately for the two different patient groups. The study was excluded from the indirect treatment comparison.

ERG notes that although Figure 3 of the ERG report states 10 trials included in network meta-analysis (NMA), the submission actually only reports two studies and the others were excluded because they were not relevant comparators for this submission.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

The searches for cost-effectiveness are included in the manufacturer's submission since the broad searches used for the major databases were suitable for identifying economic evaluations. In addition the appropriate specialist economic databases: National Health Service Health Economic Evaluation Database (NHS-HEED), Econlit, CEA Registry and Health Technology Assessment (HTA) sources were searched.

Separate searches were undertaken for the measurement and valuation of health effects and are replicated in full in Appendix 10.12 of the submission. Sources searched were extensive, including the major general health and economic databases. These search strategies were designed to retrieve utilities data for metastatic prostate cancer, combining an appropriate range of controlled vocabulary and free text terms.

No details on inclusion/exclusion criteria were available to the ERG.

Number of Source Documents

Clinical Effectiveness

Although Figure 3 in the ERG report (see the "Availability of Companion Documents" field) states 10 trials included in network meta-analysis (NMA), the submission actually only reports two studies and the others were excluded because they were not relevant comparators for this submission.

Cost-effectiveness

- No cost-effectiveness studies met the inclusion criteria.
- The manufacturer submitted an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Aberdeen Health Technology Assessment (HTA) Group (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Critique of Data Extraction

The methods used to identify and data extract current evidence are considered appropriate. Two independent reviewers screened the abstracts and full text articles identified by the literature searches. One reviewer conducted data extraction using a data extraction form designed for the review, while a second reviewer checked a sample of the data extraction. Any disagreements were resolved by a third reviewer. The company followed NICE Single Technology Appraisal (STA) guidance to conduct the risk of bias assessment. The company submission (CS) (see the "Availability of Companion Documents" field) details the information and data extracted from the included study and are considered to be generally accurate by the ERG.

Quality Assessment

The ERG performed a quality assessment of the company's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (see Table 4 in the ERG report). The quality of the systematic review was generally good.

Evidence Synthesis

As only one randomised controlled trial (RCT) was identified by the systematic review, the company could not undertake any meta-analyses.

Critique of the Indirect Comparison and/or Multiple Treatment Comparison

There are limited data on which to undertake an indirect comparison as only one trial exists for each of the enzalutamide versus placebo

(PREVAIL) and abiraterone versus placebo (COU-AA-302).

The company had undertaken a larger network meta-analysis (NMA) including studies with treatments other than enzalutamide and abiraterone. In the opinion of the ERG, the company has obtained the estimates for enzalutamide versus abiraterone from this larger network, rather than undertaking a two trial network comparison. The ERG checked the results of the company using the standard Bucher method. The ERG obtained comparable estimates for enzalutamide versus abiraterone, so although the ERG is concerned about the transparency of the methods employed by the company, the ERG is happy that the estimates obtained are accurate. However they come with the caveat of whether it is sensible to undertake an indirect comparison in the first place because of the differences in the control arms of the two trials.

See Section 4 of the ERG report and Section B of the manufacturer's submission (see the "Availability of Companion Documents" field) for more information on clinical effectiveness analysis.

Cost-effectiveness

Summary and Critique of Manufacturer's Submitted Economic Evaluation by the ERG

Model Structure

A *de novo* Markov model with a weekly cycle length was developed by the company. All patients start on a first line treatment. A proportion of those modelled as ceasing the first line treatment receive second line docetaxel, with the remainder proceeding straight to palliative care. The model has the facility for a proportion of those ceasing second line docetaxel to receive a third line treatment, with the remainder proceeding to palliative care. Those ceasing third line treatment proceed to palliative care. An equal probability of death is applied to all health states.

Treatments are also associated with skeletal-relates events (SREs) and with adverse events (AEs), these having cost and quality of life impacts.

The main model inputs are the overall survival (OS) curves and time to treatment discontinuation (TTD) curves for the first line treatments. These are derived for each of the first line treatments which are modelled:

- Enzalutamide
- Abiraterone
- Best supportive care (BSC)

The first line treatment's overall survival curve provides the probability of death in each cycle, this probability being applied equally to all the model health states. As a consequence, the modelling of treatments subsequent to the first line treatment has no impact upon the modelled overall survival. The modelling of treatments subsequent to the first line treatment only affects which health states patients pass through subsequent to first line treatment, with these health states being associated with their own costs and quality of life.

For a given first line treatment, its TTD curve determines the proportion of patients that continue to receive it and remain progression free through time.

See Section 5 of the ERG report and Section B of the manufacturer's submission (see the "Availability of Companion Documents" field) for details on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the Appraisal Consultation Document (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the Final Appraisal Determination (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The company developed a new model and needed to extrapolate overall survival (OS) and time to treatment discontinuation (TTD) from the trial data in its model.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The model structure was appropriate in terms of the sequence of treatments people would have in clinical practice in England, but there was uncertainty about whether time spent on treatments after enzalutamide reflected clinical practice.

The Committee was concerned that the company had not further checked the validity of the extrapolated data. This was particularly important because of the immaturity of the trial data and because of the small population at risk at the end of the trial follow-up (those who had not died or had been otherwise censored). This meant that a large proportion of the estimated survival benefit was based on the extrapolated period rather than the trial data.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee considered whether the model captured the benefits of delaying chemotherapy, which is important to patients. The Committee agreed that the model predicted that people having enzalutamide had more time with better utility than people on best supportive care, but it was unclear whether the benefit of delaying chemotherapy had been fully captured by the utility values included in the modelling. The Committee concluded that enzalutamide is innovative.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

None

What Are the Key Drivers of Cost-effectiveness?

The data cut-offs from PREVAIL trial that are used in the modelling and the utility value estimates.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-effectiveness Ratio [ICER])

The most plausible ICER for enzalutamide compared with best supportive care was nearer to £31,600 than to £34,800 per quality-adjusted life year (QALY) gained. The Committee also concluded that enzalutamide is innovative and taking into account factors, which had not been fully accounted for in the modelling, agreed that the ICER for enzalutamide compared with best supportive care was below £30,000 per QALY gained.

Patient Access Schemes (PPRS)

The company has agreed a patient access scheme with the Department of Health. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the National Health Service (NHS).

The company revised its patient access scheme over the course of this appraisal to increase the discount to the cost of enzalutamide for the NHS.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered evidence submitted by the manufacturer of enzalutamide and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from one randomised controlled trial (RCT). For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The PREVAIL trial showed that enzalutamide led to significantly longer overall survival and radiographic progression-free survival (rPFS) and superior tumour response, prostate-specific antigen (PSA) response, pain palliation, and quality of life compared with placebo.

Potential Harms

The most common adverse reactions with enzalutamide are tiredness, headache, hot flushes and high blood pressure.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- The recommendations in this guidance represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the National Health Service Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone-relapsed prostate cancer and the doctor responsible for their care thinks that enzalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and Astellas have agreed that enzalutamide will be available to the NHS with a patient access scheme, which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Commercial Manager at the manufacturer (commercial@astellas.com).

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan 27. 44 p. (Technology appraisal guidance; no. 377).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan 27

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan. 7 p. (Technology appraisal guidance; no. 377). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan. (Technology appraisal guidance; no. 377). Available from the NICE Web site .
- Robertson C, Cummins E, Fielding S, Lam T, Fraser C, Ramsay CR. Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. Single technology appraisal. Aberdeen (UK): Aberdeen HTA Group; 2015 Apr. 158 p. Available from the NICE Web site .
- Enzalutamide (XTANDI^{TM}) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic hormone relapsed prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Manufacturer's submission. Astellas; 2015 Mar. 373 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan. 3 p. (Technology appraisal guidance; no. 377). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on April 14, 2016.

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